Guillain-Barré syndrome, Fisher syndrome and Bickerstaff brainstem encephalitis: Understanding the pathogenesis

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Abstract

Guillain-Barré syndrome (GBS), Fisher syndrome (FS) and Bickerstaff brainstem encephalitis represent a spectrum of acute post-infectious immune-mediated diseases. GBS can present as acute inflammatory demyelinating neuropathy or acute motor axonal neuropathy (AMAN). The epidemiological association of Campylobacter jejuni infection and antiganglioside antibodies with AMAN and FS is well established. Gangliosides GM1 and GD1a, target molecules in AMAN, are identical to the terminal carbohydrate residues of C. jejuni lipo-oligosaccharides. AMAN can be reproduced in rabbits sensitized with the gangliosides and lipo-oligosaccharides, thus verifying GBS as the first example of molecular mimicry in autoimmune diseases. Immunohistochemical studies on AMAN rabbit models demonstrated autoantibody binding at the nodes of Ranvier, triggering complement activation followed by formation of membrane attack complexes. This leads to the disappearance of sodium channel clusters, causing muscle weakness and axonal degeneration. Like AMAN, FS also displays molecular mimicry but between GQ1b and C. jejuni lipo-oligosaccharides. The development of either AMAN or FS following C. jejuni infection depends on which ganglioside-like lipo-oligosaccharides are expressed by C. jejuni strains as a result of the bacterial genetic polymorphism. Bickerstaff brainstem encephalitis share common findings of anti-GQ1b antibodies with FS making the two disorders related, thus extending the spectrum of the GBS phenotype.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an immune-mediated disorder of the peripheral nerves, characterized by an acute onset of flaccid paralysis associated with the loss of reflexes. The disease is typically preceded by an infective episode and cerebrospinal fluid analysis shows albuminocytological dissociation. GBS can be classified into two major subtypes, acute inflammatory demyelinating neuropathy (AIDP) and acute motor axonal neuropathy (AMAN), affecting the peripheral nerve myelin and axons respectively. Fisher syndrome (FS) is characterized by an acute onset of ataxia, areflexia and ophthalmoplegia and when there is associated disturbance of consciousness the condition is known as Bickerstaff brainstem encephalitis (BBE). It is now recognized that these disorders share many common features, in particular the antecedent infection, the albuminocytological dissociation and also the presence of antiganglioside antibodies in certain cases. This suggests that the different syndromes are in fact part of a spectrum of immune-mediated disorder involving the peripheral nerves at one end and the central nervous system at the other. In this review, we discuss the current concepts in this group of disorders as well as how research over the last 20 years has led to the better understanding of the underlying pathogenesis in GBS and its related conditions.

THE IMPORTANT CONCEPTS IN GUILLAIN-BARRÉ SYNDROME

The significance of antecedent infections in GBS was demonstrated initially in the prospective serological studies that showed Campylobacter jejuni and cytomegalovirus infections to be significantly more frequent in patients with GBS as compared to controls. The epidemiological
association of *C. jejuni* infection with GBS and FS was established in a case control study by Rees *et al.* In that study, it was noted that patients with an antecedent *C. jejuni* infection had the more severe form of GBS with axonal degeneration. *C. jejuni*-isolated GBS peaked in 10–30-year old individuals, and the male : female ratio was 1.7 : 1. The median latent period between antecedent symptoms and the onset of neuropathy was 10 days.

Gangliosides are a large family of glycosphingolipids made up of a ceramide and sialylated oligosaccharides. They make up the components of the plasma membrane and are abundantly found in the nervous system. The ceramide moiety is anchored in the external leaflet of the lipid bilayer whilst the sialylated oligosaccharides are exposed extracellularly. The suggestion that antiganglioside antibodies may play an important role in the pathogenesis of GBS came following the report of a patient with a motor neuron disease-like disorder who had IgM anti-GM1 antibodies. It was likely that the patient had multifocal motor neuropathy, although nerve conduction studies were not described. In 1988, Ilyas *et al.* reported antiganglioside antibodies in five out of 26 GBS patients and the clinical improvement coincided with a reduction in the antibody titres. The presence of IgG anti-GM1 antibodies was later demonstrated in two patients who had AMAN associated with *C. jejuni* enteritis. Since then there have been several other gangliosides detected that appear to be target pathogenic antigens in the development of AMAN. These include GD1a, GalNAc-GD1a, and GM1b. Table 1 summarises the various reports of the frequencies of antiganglioside antibodies which appears to have a closer association with AMAN rather than AIDP. Gangliosides extracted from bovine brain had previously been used to treat various neurological disorders due to its neurotrophic effect *in vitro*. Several reports of patients developing GBS after ganglioside administration have also been reported, and IgG anti-GM1 and -GD1a antibodies were identified in some of the patients. These observations raised questions as to whether antecedent infections may also present with ganglioside mimics.

### Table 1: The percentage of antiganglioside antibodies seen in AMAN and AIDP from various studies

(Modified from Yuki N. *Muscle Nerve* 35:691–711, Copyright ©2007, John Wiley & Sons, Inc.)

<table>
<thead>
<tr>
<th>Country</th>
<th>Electrodiagnosis</th>
<th>Number of patients</th>
<th>Percentage antibody to:</th>
<th>GM1, GM1b, GD1a or GalNAc-GD1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western countries</td>
<td>AMAN AIDP</td>
<td>6/154/I19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ho <em>et al</em> (1999)</td>
<td>China</td>
<td>68/26</td>
<td>57/35</td>
<td>60</td>
</tr>
<tr>
<td>Ogawara <em>et al</em> (2000, 2003)</td>
<td>Japan</td>
<td>33/31</td>
<td>64/13</td>
<td>76</td>
</tr>
<tr>
<td>Hiraga <em>et al</em> (2005)</td>
<td>Japan</td>
<td>20/16</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>
The role of electrophysiology in Guillain-Barré syndrome

Antecedent C. jejuni infection is typically associated with AMAN. A study investigating serial electrophysiology studies in C. jejuni-positive GBS patients with diarrhoea showed that patients initially classified as AIDP based on electrophysiological criteria of prolonged distal latencies were reclassified two weeks later into AMAN as their initial distal motor latencies returned to normal. 19 In contrast, the distal latencies in typical AIDP showed a progressive increase of up to eight weeks in some cases. Therefore, it is likely that C. jejuni-related patients can show transient conduction slowing, mimicking demyelination, but the predominant electrophysiological findings are that of AMAN.

This raises questions as to how strict one should adhere to the current electrodiagnostic criteria to make a diagnosis of demyelinating neuropathy. It may be helpful for patients to have their electrophysiology studies repeated on a regular basis before classifying into the two subtypes.

The concept of molecular mimicry

Molecular mimicry postulates that the structural similarities between microbial antigens and certain host antigens lead to the autoantibodies or autoreactive T cells induced by the antecedent infections to destroy both the microbial and host targets. To conclude that a disease is triggered by molecular mimicry, four criteria should be satisfied as follows:

- Establishing an epidemiological association between the infectious agent and the immune-mediated disease
- Identifying T cells or antibodies directed against host target antigens in patients
- Identifying a microbial mimic of the target antigen
- Reproducing the disease in an animal model

In GBS patients, the association of C. jejuni infections with the presence of antiganglioside antibodies fulfills the first two criteria. Apart from IgG anti-GM1 antibodies, IgG anti-GM1b, -GD1a, and -GalNAc-GD1a antibodies have been associated with C. jejuni.21,22,23 Lipo-oligosaccharide (LOS) is a major component of the outer membrane of C. jejuni. The terminal tetrasaccharide of LOS extracted from a C. jejuni isolate of an AMAN patient was shown to be completely identical to that of the GM1 ganglioside. The findings of this study fulfilled the third criterion of molecular mimicry between GM1 gangliosides of the peripheral nerves and antecedent infectious agents in GBS.24 The same strain also expressed GD1a- as well as GM1-like LOSs.25

The animal model of AMAN was developed following sensitization of Japanese white rabbits with GM1 ganglioside. These rabbits developed acute flaccid paralysis, IgG anti-GM1 antibodies and pathological studies confirmed the characteristic features of AMAN. 26,27 A replica of AMAN was also produced by sensitizing the rabbits with GM1-like LOS of C. jejuni isolated from an AMAN patient.28 The reproduction of AMAN in the rabbit models fulfilled the final criterion for molecular mimicry. GBS provided the first verification that molecular mimicry is a cause of autoimmune disease.

The immunopathogenesis of acute motor axonal neuropathy

Voltage-gated sodium channels are localized at the nodes of Ranvier, contactin-associated protein at the paranodes, whilst voltage-gated potassium channels are present at the juxtaparanodes. There has been some controversy as to whether anti GM1 antibodies truly affect sodium channels at the nodes of Ranvier.29,30

Immunohistochemical studies performed on the peripheral nerves of AMAN rabbit models have successfully demonstrated the underlying mechanism of peripheral nerve injury in AMAN as follows.31 AMAN rabbits were studied at the acute phase (a few days after onset), early recovery (2 weeks after onset) and late recovery (4 weeks or more after onset). In the acute phase, there was lengthening of the nodes of Ranvier and IgG was noted to be deposited at some nodes where GM1 was expressed. This binding of autoantibodies triggered complement activation at the nodes and eventually, the membrane attack complex at the nodal axolemma. It is known from studies on control rabbits that the sodium channels are localised at the nodes of Ranvier in the anterior roots. Following complement activation with membrane attack complex formation in the AMAN rabbits, the sodium channel clusters are altered by the destruction of their stabilizing components which include the axonal cytoskeleton at nodes, Schwann cell microvilli and paranodal axo-glial junctions. This disruption would significantly lower the safety factor of impulse transmission causing muscle weakness in the acute phase of
unprominent. This suggests that complement activation is crucial in acute nerve injury and macrophages are the scavengers that remove the injured nerve by-products.

To summarise, in AMAN subsequent to C jejuni enteritis, infection by C jejuni bearing the GM1-like LOS can induce the production of IgG anti-GM1 antibodies. The autoantibodies bind to GM1 at the nodes of Ranvier in the spinal anterior roots, and activate complement. Membrane attack complex is formed at the nodal axolemma, which leads to “disappearance” of sodium channel clusters and disruption of axo-glial junctions. The pathological changes are able to produce muscle weakness. In severe cases, axonal degeneration occurs subsequently.

Unraveling the pathogenesis of GBS is crucial to the development of treatment options in GBS. Currently, intravenous immunoglobulin or plasma exchange is used in GBS. Given the cost of intravenous immunoglobulin and the potential complications of plasma exchange, a more rational treatment needs to be considered. Complement inhibitors such as nafamostat mesilate have long been in clinical use in Japan for the treatment of disseminated intravascular coagulation and acute pancreatitis without any serious adverse effects. Nafamostat mesilate has already been shown to be effective in the AMAN rabbits where treated rabbits showed less complement deposition and sodium channel clusters disruption when compared to the non-treated rabbits. Therefore, it would be reasonable to consider clinical trials using nafamostat mesilate or other complement inhibitors such as eculizumab.

FISHER SYNDROME

In 1956, Charles Miller Fisher described a case of acute polyneuritis with features of ophthalmoplegia, ataxia and areflexia. He postulated that the syndrome was a variant of GBS because of the presence of areflexia and CSF albuminocytological dissociation. This condition was later referred to as FS. Some patients with FS can progress to GBS, suggesting that FS is a variant of GBS. IgG anti-GQ1b antibodies were identified in patients with FS. These autoantibodies cross-react with GT1a, indicating that the terminal disialosyl structure is the epitope. An epidemiological association between C jejuni and FS was established and like AMAN, molecular mimicry was shown following the identification of GT1a-like LOS in a C jejuni isolate from a patient with Fisher syndrome.

The relationship between C jejuni infection, Fisher syndrome and acute motor axonal neuropathy

The ganglioside-like LOS in C jejuni strains are synthesized by Campylobacter sialyltransferase (Cst-II) and the gene encoding this enzyme has been cloned, cst-II. The Cst-II has 291 amino acids and the 51st determines its enzymatic activity. The C jejuni strains that express Cst-II (Thr51) can make GM1- or GD1a-like LOS; whereas, Cst-II (Asn51) strains can make GD1c- or GT1a-like LOS. The reasons why some patients with C jejuni infection develop AMAN and others FS lie in this genetic polymorphism. GM1 and GD1a have been shown to be expressed on motor nerve axons whilst GQ1b is highly expressed in the oculomotor nerves and limb muscle spindles. Cst-II (Thr51) strains produce GM1- or GD1a-like LOSs, inducing the production of IgG anti-GM1 or -GD1a antibodies. Subsequent to the autoantibody binding, patients go on to develop limb weakness in the form of AMAN. In contrast, Cst-II (Asn51) strains produce GD1c- or GT1a-like LOS, inducing the production of IgG anti-GQ1b antibodies. Therefore, following the binding of these autoantibodies, patients develop ophthalmoplegia and ataxia as seen in FS (Figure 1).

BICKERSTAFF BRAINSTEM ENCEPHALITIS

In 1951, Bickerstaff reported 3 cases and later added 5 cases of brain-stem encephalitis with benign outcomes. All the patients reported showed drowsiness in addition to ophthalmoplegia and ataxia. Like Fisher, Bickerstaff initially speculated the aetiology as being similar to GBS because of the presence of antecedent infection, areflexia and CSF albuminocytological dissociation. However, an assessment of 18 such patients led the Bickerstaff group to reject their hypothesis that this could be a GBS variant based on the radiological and pathological changes seen in the central nervous system.

If one were to look back at the original case report of Fisher, one of the three patients he described also had drowsiness. The presence of anti-GQ1b antibody in three patients with BBE also indicated that BBE and FS are closely related. Along with this, there were patients with BBE who also had an AMAN type of limb weakness, suggesting that AMAN and BBE...
Campylobacter jejuni

Cst-II (Thr51/Asn51)  Cst-II (Asn51)

GM1-like LOS  GD1a-like LOS  GT1a-like LOS  GD1c-like LOS

Anti-GM1 or anti-GD1a IgG antibodies  Anti-GQ1b IgG antibodies

GM1  GD1a  GQ1b

Neuromuscular junctions in limb muscles  Anterior roots  Neuromuscular junctions in extraocular muscles

Limb weakness

Acute Motor Axonal Neuropathy  Ophthalmoparesis or Ataxia  Muscle spindles  Fisher syndrome  Bickerstaff brainstem encephalitis

Human

Galactose  Glucose  N-Acetylgalactosamine  N-Acety neuraminic acid  Cer  Ceramide

Figure 1: Campylobacter jejuni gene polymorphism influences the clinical pattern that follows the infection. C. jejuni carrying Cst-II (Thr51) can express GM1-like or GD1a-like lipo-oligosaccharide (LOS) on its cell surface. Infection by such a strain may induce IgG anti-GM1 or anti-GD1a antibodies in some patients. IgG anti-GM1 and -GD1a antibodies respectively bind to GM1 and GD1a that are expressed on motor nerves of the four limbs, inducing acute motor axonal neuropathy. In contrast, C. jejuni that carries Cst-II (Asn51) express GT1a- or GD1c-like LOS on their cell surface, and may induce IgG anti-GQ1b antibody production in some patients. IgG anti-GQ1b antibodies bind to GQ1b expressed on oculomotor nerves, muscle spindles in the limbs or reticular formation in the brainstem, inducing Fisher syndrome or Bickerstaff brainstem encephalitis. Modified from Muscle Nerve 35:691-711, Copyright ©2007, John Wiley & Sons, Inc.
are also related. A study where the laboratory findings between 53 BBE patients were compared to 466 FS patients provided further proof of the Fisher-Bickerstaff continuum. Both groups of patients had similar laboratory findings; positive anti-GQ1b antibodies (68% versus 83%), CSF albuminoctological dissociation (25% versus 37%), CSF pleocytosis (32% versus 4%) and slow waves in EEG (57% versus 25%). These findings offer conclusive evidence that FS and BBE form a continuous spectrum with variable peripheral nervous system and central nervous system involvement. It is likely that IgG anti-GQ1b antibodies are able bind to muscle spindles, neuromuscular junctions in extraocular muscles or brainstem reticular formation, and induce the development of ataxia, ophthalmoplegia or impaired consciousness. Although not widely accepted, a new term “Fisher–Bickerstaff syndrome” may be helpful to understand the nosological relationship between the two syndromes.

CONCLUSION

Despite the progress made in the understanding of the pathogenesis of AMAN, FS and BBE, there are still unanswered questions in GBS. For instance, the target antigen in AIDP is yet to be elucidated. Factors inherent to the host are likely to influence the development of GBS and its related conditions in a proportion of infected patients. Epidemiological studies have already suggested geographical variation in the disease presentation and there may also be host genetic factors involved. It is hoped that further research into these key areas of GBS will address some of the unresolved issues thus allowing more effective therapeutic interventions to be developed.

REFERENCES

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